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Dated 22 July 2003

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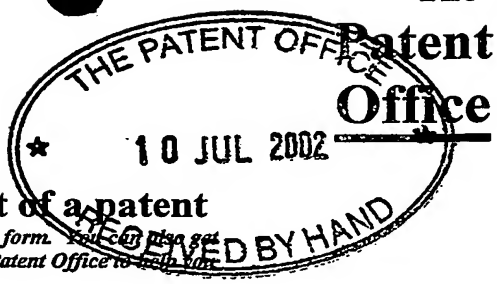

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P01/7700 0.00-0215978.8

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
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1. Your reference P707399GB(KB523GB)/48154.

2. Patent application number
(The Patent Office will fill in this part) 10 JUL 2002 0215978.8

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Karo Bio AB
Novum
SE-141 57 Huddinge
Sweden

06477841002

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation: Sweden

4. Title of the invention: Novel Compounds

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*:

WITHERS & ROGERS
Goldings House
2 Hays Lane
London
SE1 2HW

Patents ADP number *(if you know it)*: 1776001 ✓

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*
-	-	-

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*
-	-

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(answer 'Yes' if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	33
Claim(s)	05
Abstract	01
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Priority documents	-
Translations of priority documents	-
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	-
Request for preliminary examination and search *(Patents Form 9/77)*	01
Request for substantive examination *(Patents Form 10/77)*	-
Any other documents *(please specify)*	-

11. I/We request the grant of a patent on the basis of this application.

Signature Wilson Gunn Date 6 July 2007

12. Name and daytime telephone number of person to contact in the United Kingdom — David G Bannerman — 01926 336111

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KB523GB

NOVEL COMPOUNDS

FIELD OF THE INVENTION

This invention relates to novel compounds that are thyroid receptor ligands and are preferably selective for the thyroid hormone receptor β. Further, the present invention relates to methods for using such compounds and to pharmaceutical compositions containing such compounds.

BACKGROUND OF THE INVENTION

While the extensive role of thyroid hormones in regulating metabolism in humans is well recognized, the discovery and development of new specific drugs for improving the treatment of hyperthyroidism and hypothyroidism has been slow. This has also limited the development of thyroid hormone agonists and antagonists for treatment of other important clinical indications, such as hypercholesterolemia, obesity and cardiac arrhythmias.

Thyroid hormones affect the metabolism of virtually every cell of the body. At normal levels, these hormones maintain body weight, the metabolic rate, body temperature, and mood, and influence serum low-density lipoprotein (LDL) levels. Thus, in hypothyroidism there is weight gain, high levels of LDL cholesterol, and depression. In excess with hyperthyroidism, these hormones lead to weight loss, hypermetabolism, lowering of serum LDL levels, cardiac arrhythmias, heart failure, muscle weakness, bone loss in postmenopausal women, and anxiety.

Thyroid hormones are currently used primarily as replacement therapy for patients with hypothyroidism. Therapy with L-thyroxine returns metabolic functions to normal and can easily be monitored with routine serum measurements of levels of thyroid-stimulating hormone (TSH), thyroxine (3,5,3',5'-tetraiodo-L-thyronine, or T_4) and triiodothyronine (3,5,3'-triiodo-L-thyronine, or T_3). However, certain detrimental effects from thyroid hormones may restrict replacement therapy, particularly in older

individuals. In addition, some effects of thyroid hormones may be therapeutically useful in non-thyroid disorders if adverse effects can be minimized or eliminated. These potentially useful influences include weight reduction, lowering of serum LDL levels, amelioration of depression and stimulation of bone formation. Prior attempts to utilize thyroid hormones pharmacologically to treat these disorders have been limited by manifestations of hyperthyroidism, and in particular by cardiovascular toxicity.

Development of specific and selective thyroid hormone receptor agonists could lead to specific therapies for these common disorders while avoiding the cardiovascular and other toxicities of native thyroid hormones. Tissue-selective thyroid hormone agonists may be obtained by selective tissue uptake or extrusion, topical or local delivery, targeting to cells through other ligands attached to the agonist and targeting receptor subtypes. Thyroid hormone receptor agonists that interact selectively with the β-form of the thyroid hormone receptor offer an especially attractive method for avoiding cardio-toxicity.

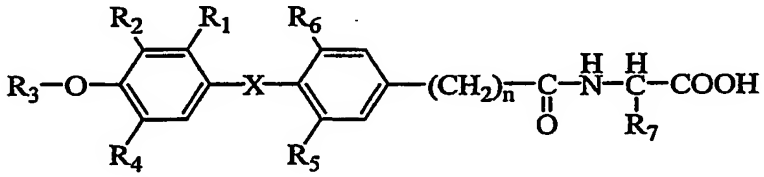
Thyroid hormone receptors (TRs) are, like other nuclear receptors, single polypeptide chains. The various receptor forms appear to be products of two different genes, α and β. Further isoform differences are due to the fact that differential RNA processing results in at least two isoforms from each gene. The $TR\alpha_1$, $TR\beta_1$ and $TR\beta_2$ isoforms bind thyroid hormone and act as ligand-regulated transcription factors. In adults, the $TR\beta_1$ isoform is the most prevalent form in most tissues, especially in the liver and muscle. The $TR\alpha_2$ isoform is prevalent in the pituitary and other parts of the central nervous system, does not bind thyroid hormones, and acts in many contexts as a transcriptional repressor. The $TR\alpha_1$ isoform is also widely distributed, although its levels are generally lower than those of the $TR\beta_1$ isoform. This isoform may be especially important for development. Whereas many mutations in the TRβ gene have been found and lead to the syndrome of generalized resistance to thyroid hormone, mutations leading to impaired TRα function have not been found.

A growing body of data suggests that many or most effects of thyroid hormones on the heart, and in particular, on the heart rate and rhythm, are mediated through the α-form

of the TRα_1 isoform, whereas most actions of the hormone such as on the liver, muscle and other tissues, are mediated more through the β-forms of the receptor. Thus, a TRβ-selective agonist might not elicit the cardiac rhythm and rate influences of the hormones, but would elicit many other actions of the hormones. We believe that the α-form of the receptor is primarily associated with heart rate function for the following reasons: (i) tachycardia is very common in the syndrome of generalized resistance to thyroid hormone in which there are defective TRβ-forms, and high circulating levels of T_4 and T_3; (ii) there was tachycardia in the only described patient with a double deletion of the TRβ gene (Takeda et al, *J. Clin. Endrocrinol. & Metab.* 1992, *74*, p49); (iii) a double knockout TRα gene (but not β-gene) mouse has a slower pulse than control mice (Forrest D and Vennstrom B, *Thyroid* 2000, *10(1)*, 41-52); (iv) western blot analysis of human myocardial TRs show presence of the TRα_1, TRα_2 and TRβ_2 proteins, but not TRβ_1. If these indications are correct, then it may be possible that a TRβ-selective agonist could be used to mimic a number of thyroid hormone actions, while having a lesser effect on the heart. Such a compound may be used for: (i) replacement therapy in elderly subjects with hypothyroidism who are at risk for cardiovascular complications; (ii) replacement therapy in elderly subjects with subclinical hypothyroidism who are at risk for cardiovascular complications; (iii) obesity; (iv) hypercholesterolemia due to elevations of plasma LDL levels; (v) depression; (vi) osteoporosis in combination with a bone resorption inhibitor.

SUMMARY OF THE INVENTION

In accordance with the present invention, compounds are provided which are thyroid receptor ligands, and have the general formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

R_1 and R_2 are independently selected from: hydrogen, fluorine, chlorine, bromine, nitrile (-CN), C_{1-2} alkyl, said alkyl substituted with 0, 1, 2 or 3 R^a groups which may be the same or different, and with the proviso that R_1 and R_2 are not both hydrogen.

R_3 is selected from: hydrogen, C_{1-6} alkyl or benzyl, said alkyl or benzyl being substituted with 0, 1, 2 or 3 R^a groups which may be the same or different;

R_4 is selected from: halogen; C_{1-4} alkyl, C_{3-4} cycloalkyl, C_{2-4} alkenyl and C_{2-4} alkynyl, said alkyl, cycloalkyl, alkenyl and alkynyl being substituted with 0, 1, 2 or 3 R^a groups which may be the same or different;

R_5 and R_6 are the same or different and are independently selected from: chlorine, bromine, and C_{1-4} alkyl;

R_7 is selected from: hydrogen; C_{1-4} alkyl, C_{3-4} cycloalkyl, C_{2-4} alkenyl and C_{2-4} alkynyl, said alkyl, cycloalkyl, alkenyl and alkynyl being substituted with 0, 1, 2 or 3 R^a groups which may be the same or different;

R^a is fluorine, chlorine or bromine;

n is 0, 1 or 2;

X is selected from: -O-, -S-, -SO-, $-SO_2-$, $-SO_2NH-$ and $-SO_2O-$;

The definition of formula I above includes all prodrug-esters, stereoisomers and pharmaceutically acceptable salts of formula I.

The compounds of formula I are thyroid hormone receptor ligands and include compounds which are, for example, selective agonists, partial agonists, antagonists or partial antagonists of the thyroid receptor. Preferably, the compounds of formula I possess activity as agonists of the thyroid receptor, preferably selective agonists of the

thyroid receptor-beta, and may be used in the treatment of diseases or disorders associated with thyroid receptor activity. In particular, the compounds of formula I may be used in the treatment of diseases or disorders associated with metabolic dysfunction or which are dependent upon the expression of a T_3 regulated gene, such as obesity, hypercholesterolemia, atherosclerosis, cardiac arrhythmias, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer, glaucoma, skin disorders or diseases and congestive heart failure.

The present invention provides for compounds of formula I, pharmaceutical compositions employing such compounds and for methods of using such compounds. In particular, the present invention provides for a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I, alone or in combination with a pharmaceutically acceptable carrier.

Further, in accordance with the present invention, a method is provided for preventing, inhibiting or treating the progression or onset of diseases or disorders associated with the thyroid receptor, particularly, the thyroid receptor-beta, such as the diseases or disorders defined above and hereinafter, wherein a therapeutically effective amount of a compound of formula I is administered to a mammalian, i.e., human patient in need of treatment.

The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more other agent(s) active in the therapeutic areas described herein.

In addition, a method is provided for preventing, inhibiting or treating the diseases as defined above and hereinafter, wherein a therapeutically effective amount of a combination of a compound of formula I and another compound of the invention and/or another type of therapeutic agent, is administered to a mammalian patient in need of treatment.

Compounds of the invention include, but are not limited to, the following:

N-[3,5-Dichloro-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)benzoyl] glycine (**E1**);
N-[3,5-Dichloro-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (**E2**);
N-[3,5-Dichloro-4-(2-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (**E3**);
N-[3,5-Dichloro-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (**E4**);
N-[3,5-Dichloro-4-(3-cyano-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (**E5**);
N-[3,5-Dichloro-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (**E6**).

DETAILED DESCRIPTION OF THE INVENTION

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

The term "thyroid receptor ligand" as used herein is intended to cover any moiety, which binds to a thyroid receptor. The ligand may act as an agonist, an antagonist, a partial agonist or a partial antagonist. Another term for "thyroid receptor ligand" is "thyromimetic".

The term "alkyl" as employed herein alone or as part of another group refers to an acyclic straight or branched chain radical, containing 1, 2, 3 or 4 carbons, preferably 1, 2 or 3 carbons in the normal chain, i.e. methyl, ethyl, propyl. When a substituted alkyl is present, this refers to a straight or branched alkyl group substituted with 1, 2 or 3 R^a groups (which may be the same or different) at any available point, as defined with respect to each variable.

The term "substituted alkyl" includes an alkyl group optionally substituted with one or more functional groups which are commonly attached to such chains, such as, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, hydroxy, cyano, nitro, amino, halo, carboxyl or alkyl ester thereof and/or carboxamide, substituted or unsubstituted.

The term "alkenyl" as used herein by itself or as part of another group refers to a straight or branched chain radical of 2, 3 or 4 carbons and at least one carbon-to-carbon

double bond. Preferably only one carbon-to-carbon double bond is present. Preferably 2 or 3 carbons are present in the normal chain radical, such as ethenyl and propenyl. As described above with respect to the "alkyl", the straight or branched portion of the alkenyl group may be optionally substituted by 1, 2 or 3 R^a groups (which may be the same or different) when a substituted alkenyl group is provided.

The term "alkynyl" as used herein by itself or as part of another group refers to a straight or branched chain radical of 2 to 4 carbons and at least one carbon-to-carbon triple bond. Preferably only one carbon-to-carbon triple bond is present. Preferably 2 to 3 carbons are present in the normal chain, such as ethynyl and propynyl. As described above with respect to "alkyl", the straight portion of the alkynyl group may be optionally substituted by 1, 2 or 3 R^a groups (which may be the same or different) when a substituted alkynyl group is provided.

The term "cycloalkyl" as employed herein alone or as part of another group refers to a saturated cyclic hydrocarbon group or partially unsaturated cyclic hydrocarbon group, independently containing one carbon-to-carbon double bond. The cyclic hydrocarbon contains 3 to 4 carbons. It should also be understood that the present invention also involves cycloalkyl rings where 1 to 2 carbons in the ring are replaced by either -O-, -S- or -N-, thus forming a saturated or partially saturated heterocycle. Examples of such rings are aziridine, thiiranes and the like. Preferred heterocyclic rings are 3-membered, which may be optionally substituted by 1, 2 or 3 R^a groups (which may be the same or different) through available carbons as in the case of "alkyl". Preferred cycloalkyl groups include 3 carbons, such as cyclopropyl, which may be optionally substituted by 1, 2 or 3 R^a groups (which may be the same or different) through available carbons as in the case of "alkyl".

The term "halogen" refers to fluorine, chlorine, bromine and iodine. When R_2 is selected from alkyl, and is substituted with 1, 2 or 3 R^a groups, the preferred substituents include fluorine, thus forming substituents such as $-CF_3$ and $-CHF_2$.

The term "benzyl" refers to a radical consisting of a methylene group ($-CH_2-$) connected at one position to a benzene ring ($-CH_2-C_6H_6$)

The compounds of formula I can be present as salts, which are also within the scope of this invention. Pharmaceutically-acceptable (i.e., non-toxic, physiologically-acceptable) salts are preferred. If the compounds of formula I have, for example, at least one basic center, they can form acid addition salts. These are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted, for example, by halogen, for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, (for example aspartic or glutamic acid or lysine or arginine), or benzoic acid, or with organic sulfonic acids, such as (C_1-C_4) alkyl or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for example methyl- or p-toluene- sulfonic acid. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The compounds of formula I having at least one acid group (for example COOH) can also form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono, di or tri-lower alkylamine, for example ethyl, tertbutyl, diethyl, diisopropyl, triethyl, tributyl or dimethyl-propylamine, or a mono, di or trihydroxy lower alkylamine, for example mono, di or triethanolamine. Corresponding internal salts may furthermore be formed. Salts that are unsuitable for pharmaceutical uses but which can be employed, for example, for the isolation or purification of free compounds of formula I or their pharmaceutically-acceptable salts, are also included. Preferred salts of the compounds of formula I which contain a basic group include monohydrochloride, hydrogensulfate, methanesulfonate, phosphate or nitrate. Preferred salts of the compounds of formula I which contain an acid group include sodium, potassium and magnesium salts and pharmaceutically-acceptable organic amines.

The compounds of formula I may also have prodrug forms. Any compound that will be converted in vivo to provide the bioactive agent (i.e., the compound of formula I) is a prodrug within the scope and spirit of the invention.

Various forms of prodrugs are well known in the art. A comprehensive description of prodrugs and prodrug derivatives may be found in: (i) *The Practice of Medicinal Chemistry*, Camille G. Wermuth et al., Ch 31, (Academic Press, 1996); (ii) *Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, 1985); and (iii) *A Textbook of Drug Design and Development*, P. Krogsgaard–Larson and H. Bundgaard, eds. Ch 5, pgs 113 – 191 (Harwood Academic Publishers, 1991). Said references are incorporated herein by reference.

Embodiments of prodrugs suitable for use in the present invention include lower alkyl esters, such as ethyl ester, or acyloxyalkyl esters such as pivaloyloxymethyl (POM).

An administration of a therapeutic agent of the invention includes administration of a therapeutically effective amount of the agent of the invention. The term "therapeutically effective amount" as used herein refers to an amount of a therapeutic agent to treat or prevent a condition treatable by administration of a composition of the invention. That amount is the amount sufficient to exhibit a detectable therapeutic or preventative or ameliorative effect. The effect may include, for example, treatment or prevention of the conditions listed herein. The precise effective amount for a subject will depend upon the subject's size and health, the nature and extent of the condition being treated, recommendations of the treating physician, and the therapeutics or combination of therapeutics selected for administration. Thus, it is not useful to specify an exact effective amount in advance.

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one of the R substitutents. Consequently, compounds of formula I can exist in enantiomeric or diasteromeric forms or in mixtures thereof. The processes for preparation can utilize

racemates, enantiomers or diasteromers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods. For example, chromatographic or fractional crystallization.

UTILITIES & COMBINATIONS

UTILITIES: The compounds of the present invention are thyroid receptor ligands, and include compounds that are, for example, selective agonists, partial agonists, antagonists or partial antagonists of the thyroid receptor. Preferably compounds of the present invention possess activity as agonists of the thyroid receptor, preferably selective agonists of the thyroid receptor-beta, and may be used in the treatment of diseases or disorders associated with thyroid receptor activity. In particular, compounds of the present invention may be used in the treatment of diseases or disorders associated with metabolism dysfunction or which are dependent upon the expression of a T_3 regulated gene.

Accordingly, the compounds of the present invention can be administered to mammals, preferably humans, for the treatment of a variety of conditions and disorders, including, but not limited to hypothyroidism; subclinical hyperthyroidism; non-toxic goiter; atherosclerosis; thyroid hormone replacement therapy (e.g., in the elderly); malignant tumor cells containing the thyroid receptor; papillary or follicular cancer; maintenance of muscle strength and function (e.g., in the elderly); reversal or prevention of frailty or age-related functional decline ("ARFD") in the elderly (e.g., sarcopenia); treatment of catabolic side effects of glucocorticoids; prevention and/or treatment of reduced bone mass, density or growth (e.g., osteoporosis and osteopenia); treatment of chronic fatigue syndrome (CFS); accelerating healing of complicated fractures, e.g. distraction osteogenesis; in joint replacement; eating disorders (e.g., anorexia); treatment of obesity and growth retardation associated with obesity; treatment of depression, nervousness, irritability and stress; treatment of reduced mental energy and low self-esteem (e.g., motivation/assertiveness); improvement of cognitive function (e.g., the treatment of dementia, including Alzheimer's disease and short term memory loss); treatment of catabolism in connection with pulmonary dysfunction and ventilator dependency;

treatment of cardiac dysfunction (e.g., associated with valvular disease, myocardial infarction, cardiac hypertrophy or congestive heart failure); lowering blood pressure; protection against ventricular dysfunction or prevention of reperfusion events; treatment of hyperinsulinemia; stimulation of osteoblasts, bone remodeling and cartilage growth; regulation of food intake; treatment of insulin resistance, including NIDDM, in mammals (e.g., humans); treatment of insulin resistance in the heart; treatment of congestive heart failure; treatment of musculoskeletal impairment (e.g., in the elderly); improvement of the overall pulmonary function; skin disorders or diseases, such as glucocorticoid induced dermal atrophy, including restoration of dermal atrophy induced by topical glucocorticoids, and the prevention of dermal atrophy induced by topical glucocorticoids (such as the simultaneous treatment with topical glucocorticoid or a pharmacological product including both glucocorticoid and a compound of the invention), the restoration/prevention of dermal atrophy induced by systemic treatment with glucocorticoids, restoration/prevention of atrophy in the respiratory system induced by local treatment with glucocorticoids, UV-induced dermal atrophy, dermal atrophy induced by aging (wrinkles, etc.), wound healing, keloids, stria, cellulite, roughened skin, actinic skin damage, lichen planus, ichtyosis, acne, psoriasis, Dernier's disease, eczema, atopic dermatitis, chloracne, pityriasis and skin scarring.
The term treatment is also intended to include prophylactic treatment. In addition, the conditions, diseases, and maladies collectively referenced to as "Syndrome X" or Metabolic Syndrome as detailed in Johannsson *J. Clin. Endocrinol. Metab.*, 82, 727-34 (1997), may be treated employing the compounds of the invention.

COMBINATIONS: The present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, a therapeutically effective amount of at least one of the compounds of formula I, alone or in combination with a pharmaceutical carrier or diluent. Optionally, compounds of the present invention can be used alone, in combination with other compounds of the invention, or in combination with one or more other therapeutic agent(s), e.g., an antidiabetic agent or other pharmaceutically active material.

The compounds of the present invention may be employed in combination with other modulators and/or ligands of the thyroid receptor or other suitable therapeutic agents useful in the treatment of the aforementioned disorders including: anti-diabetic agents; anti-osteoporosis agents; anti-obesity agents; growth promoting agents (including growth hormone secretagogues); anti-inflammatory agents; anti-anxiety agents; anti-depressants; anti-hypertensive agents; cardiac glycosides; cholesterol/lipid lowering agents; appetite suppressants; bone resorption inhibitors; thyroid mimetics (including other thyroid receptor agonists); anabolic agents; and anti-tumor agents.

Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include biguanides (e.g., metformin or phenformin), glucosidase inhibitors (e.g,. acarbose or miglitol), insulins (including insulin secretagogues or insulin sensitizers), meglitinides (e.g., repaglinide), sulfonylureas (e.g., glimepiride, glyburide, gliclazide, chlorpropamide and glipizide), biguanide/glyburide combinations (e.g., Glucovance®), thiazolidinediones (e.g., troglitazone, rosiglitazone and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, SGLT2 inhibitors, glycogen phosphorylase inhibitors, inhibitors of fatty acid binding protein (aP2), glucagon-like peptide-1 (GLP-1), and dipeptidyl peptidase IV (DP4) inhibitors.

Examples of suitable anti-osteoporosis agents for use in combination with the compounds of the present invention include alendronate, risedronate, PTH, PTH fragment, raloxifene, calcitonin, RANK ligand antagonists, calcium sensing receptor antagonists, TRAP inhibitors, selective estrogen receptor modulators (SERM) and AP-1 inhibitors.

Examples of suitable anti-obesity agents for use in combination with the compounds of the present invention include aP2 inhibitors, PPAR gamma antagonists, PPAR delta agonists, beta 3 adrenergic agonists, such as AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer) or other known beta 3 agonists as disclosed in U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 and 5,488,064, a lipase inhibitor, such as orlistat or ATL-962 (Alizyme), a serotonin (and dopamine) reuptake

inhibitor, such as sibutramine, topiramate (Johnson & Johnson) or axokine (Regeneron), other thyroid receptor beta drugs, such as a thyroid receptor ligand as disclosed in WO 97/21993 (U. Cal SF), WO 99/00353 (KaroBio) and GB98/284425 (KaroBio), CB-1 (cannabinoid receptor) antagonists (see G. Colombo et al, "Appetite Suppression and Weight Loss After the Cannabionid Antagonist SR 141716", Life Sciences, Vol 63, PL 113-117 (1998)) and/or an anorectic agent, such as dexamphetamine, phentermine, phenylpropanolamine or mazindol.

The compounds of the present invention may be combined with growth promoting agents, such as, but not limited to, TRH, diethylstilbesterol, theophylline, enkephalins, E series prostaglandins, compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeranol, and compounds disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox or peptides disclosed in U.S. Patent No. 4,411,890.

The compounds of the invention may also be used in combination with growth hormone secretagogues such as GHRP-6, GHRP-1 (as described in U.S. Patent No. 4,411,890 and publications WO 89/07110 and WO 89/07111), GHRP-2 (as described in WO 93/04081), NN703 (Novo Nordisk), LY444711 (Lilly), MK-677 (Merck), CP424391 (Pfizer) and B-HT920, or with growth hormone releasing factor and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2, or with alpha-adrenergic agonists, such as clonidine or serotinin 5-HT_D agonists, such as sumatriptan, or agents which inhibit somatostatin or its release, such as physostigmine and pyridostigmine. A still further use of the disclosed compounds of the invention is in combination with parathyroid hormone, PTH(1-34) or bisphosphonates, such as MK-217 (alendronate).

A still further use of the compounds of the invention is in combination with estrogen, testosterone, a selective estrogen receptor modulator, such as tamoxifen or raloxifene, or other androgen receptor modulators, such as those disclosed in Edwards, J. P. et al., *Bio. Med. Chem. Let.*, 9, 1003-1008 (1999) and Hamann, L. G. et al., *J. Med. Chem.*, 42, 210-212 (1999).

A further use of the compounds of this invention is in combination with steriodal or non-steroidal progesterone receptor agonists ("PRA"), such as levonorgestrel, medroxyprogesterone acetate (MPA).

Examples of suitable anti-inflammatory agents for use in combination with the compounds of the present invention include prednisone, dexamethasone, Enbrel®, cyclooxygenase inhibitors (i.e., COX-1 and/or COX-2 inhibitors such as NSAIDs, aspirin, indomethacin, ibuprofen, piroxicam, Naproxen®, Celebrex®, Vioxx®), CTLA4-Ig agonists/antagonists, CD40 ligand antagonists, IMPDH inhibitors, such as mycophenolate (CellCept®), integrin antagonists, alpha-4 beta-7 integrin antagonists, cell adhesion inhibitors, interferon gamma antagonists, ICAM-1, tumor necrosis factor (TNF) antagonists (e.g., infliximab, OR1384), prostaglandin synthesis inhibitors, budesonide, clofazimine, CNI-1493, CD4 antagonists (e.g., priliximab), p38 mitogen-activated protein kinase inhibitors, protein tyrosine kinase (PTK) inhibitors, IKK inhibitors, and therapies for the treatment of irritable bowel syndrome (e.g., Zelmac® and Maxi-K® openers such as those disclosed in U.S. Patent No. 6,184,231 B1).

Example of suitable anti-anxiety agents for use in combination with the compounds of the present invention include diazepam, lorazepam, buspirone, oxazepam, and hydroxyzine pamoate.

Examples of suitable anti-depressants for use in combination with the compounds of the present invention include citalopram, fluoxetine, nefazodone, sertraline, and paroxetine.

For the treatment of skin disorders or diseases as described above, the compounds of the present invention may be used alone or optionally in combination with a retinoid, such as tretinoin, or a vitamin D analog.

Examples of suitable anti-hypertensive agents for use in combination with the compounds of the present invention include beta adrenergic blockers, calcium channel

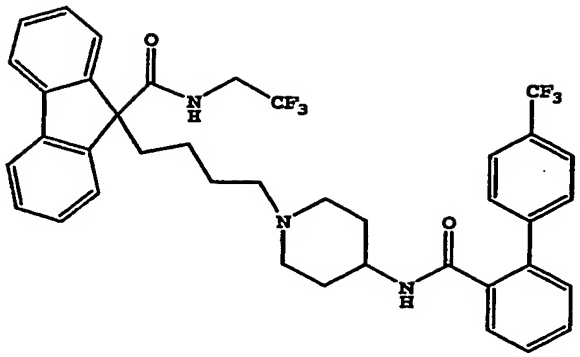
blockers (L-type and T-type; e.g. diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diuretics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrenene, amiloride, spironolactone), renin inhibitors, ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-1 receptor antagonists (e.g., losartan, irbesartan, valsartan), ET receptor antagonists (e.g., sitaxsentan, atrsentan and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265), Dual ET/AII antagonist (e.g., compounds disclosed in WO 00/01389), neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat and gemopatrilat), and nitrates.

Examples of suitable cardiac glycosides for use in combination with the compounds of the present invention include digitalis and ouabain.

Examples of suitable cholesterol/lipid lowering agents for use in combination with the compounds of the present invention include HMG-CoA reductase inhibitors, squalene synthetase inhibitors, fibrates, bile acid sequestrants, ACAT inhibitors, MTP inhibitors, lipooxygenase inhibitors, an ileal Na^+/bile acid cotransporter inhibitor, cholesterol absorption inhibitors, and cholesterol ester transfer protein inhibitors (e.g., CP-529414).

MTP inhibitors which may be employed herein in combination with one or more compounds of formula I include MTP inhibitors as disclosed in U.S. Patent No. 5,595,872, U.S. Patent No. 5,739,135, U.S. Patent No. 5,712,279, U.S. Patent No. 5,760,246, U.S. Patent No. 5,827,875, U.S. Patent No. 5,885,983 and U.S. Patent No. 5,962,440 all incorporated herein by reference.

A preferred MTP inhibitor is
9-[4-[4-[[2-(2,2,2-Trifluoroethoxy)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide:



The HMG CoA reductase inhibitors which may be employed in combination with one or more compounds of formula I include mevastatin and related compounds as disclosed in U.S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds as disclosed in U.S. Patent No. 4,231,938, pravastatin and related compounds such as disclosed in U.S. Patent No. 4,346,227, simvastatin and related compounds as disclosed in U.S. Patent Nos. 4,448,784 and 4,450,171. Further HMG CoA reductase inhibitors which may be employed herein include fluvastatin, disclosed in U.S. Patent No. 5,354,772, cerivastatin disclosed in U.S. Patent Nos. 5,006,530 and 5,177,080, atorvastatin disclosed in U.S. Patent Nos. 4,681,893, 5,273,995, 5,385,929 and 5,686,104, pyrazole analogs of mevalonolactone derivatives as disclosed in U.S. Patent No. 4,613,610, indene analogs of mevalonolactone derivatives, as disclosed in PCT application WO 86/03488, 6-[2-(substituted-pyrrol-1-yl)-alkyl)pyran-2-ones and derivatives thereof, as disclosed in U.S. Patent No. 4,647,576, Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone, as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives, as disclosed in French Patent No. 2,596,393, 2,3-disubstituted pyrrole, furan and thiophene derivatives, as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone, as disclosed in U.S. Patent No. 4,686,237, octahydronaphthalenes, such as disclosed in U.S. Patent No. 4,499,289, keto analogs of mevinolin (lovastatin), as disclosed in European Patent Application No.0,142,146 A2, as well as other known HMG CoA reductase inhibitors.

The squalene synthetase inhibitors which may be used in combination with the compounds of the present invention include, but are not limited to, α-phosphono-sulfonates disclosed in U.S. Patent No. 5,712,396, those disclosed by Biller et al, J. Med. Chem., 1988, Vol. 31, No. 10, pp 1869-1871, including isoprenoid (phosphinylmethyl)phosphonates, terpenoid pyrophosphates disclosed by P. Ortiz de Montellano et al, J. Med. Chem., 1977, 20, 243-249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, J. Am. Chem. Soc., 1976, 98, 1291-1293, phosphinylphosphonates reported by McClard, R.W. et al, J.A.C.S., 1987, 109, 5544 and cyclopropanes reported by Capson, T.L., PhD dissertation, June, 1987, Dept. Med. Chem. U of Utah, Abstract, Table of Contents, pp 16, 17, 40-43, 48-51, as well as other squalene synthetase inhibitors as disclosed in U.S. Patent No. 4,871,721 and 4,924,024 and in Biller, S.A., Neuenschwander, K., Ponpipom, M.M., and Poulter, C.D., Current Pharmaceutical Design, 2, 1-40 (1996).

Bile acid sequestrants which may be used in combination with the compounds of the present invention include cholestyramine, colestipol and DEAE-Sephadex (Secholex®, Policexide®), as well as lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphos-phorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives), nicotinic acid, acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives such as disclosed in U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.

ACAT inhibitors suitable for use in combination with compounds of the invention include ACAT inhibitors as described in, Drugs of the Future 24, 9-15 (1999), (Avasimibe); "The ACAT inhibitor, Cl-1011 is effective in the prevention and regression of aortic fatty streak area in hamsters", Nicolosi et al, Atherosclerosis (Shannon, Irel). (1998), 137(1), 77-85; "The pharmacological profile of FCE 27677: a

novel ACAT inhibitor with potent hypolipidemic activity mediated by selective suppression of the hepatic secretion of ApoB100-containing lipoprotein", Ghiselli, Giancarlo, Cardiovasc. Drug Rev. (1998), 16(1), 16-30; "RP 73163: a bioavailable alkylsulfinyl-diphenylimidazole ACAT inhibitor", Smith, C., et al, Bioorg. Med. Chem. Lett. (1996), 6(1), 47-50; "ACAT inhibitors: physiologic mechanisms for hypolipidemic and anti-atherosclerotic activities in experimental animals", Krause et al, Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Mannfred A., Inflammation: Mediators Pathways (1995), 173-98, Publisher: CRC, Boca Raton, Fla.; "ACAT inhibitors: potential anti-atherosclerotic agents", Sliskovic et al, Curr. Med. Chem. (1994), 1(3), 204-25; "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first water-soluble ACAT inhibitor with lipid-regulating activity. Inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). 7. Development of a series of substituted N-phenyl-N'-[(1-phenylcyclopentyl)methyl]ureas with enhanced hypocholesterolemic activity", Stout et al, Chemtracts: Org. Chem. (1995), 8(6), 359-62.

Examples of suitable cholesterol absorption inhibitor for use in combination with the compounds of the invention include SCH48461 (Schering-Plough), as well as those disclosed in Atherosclerosis 115, 45-63 (1995) and J. Med. Chem. 41, 973 (1998).

Examples of suitable ileal Na^+/bile acid cotransporter inhibitors for use in combination with the compounds of the invention include compounds as disclosed in Drugs of the Future, 24, 425-430 (1999).

Examples of suitable thyroid mimetics for use in combination with the compounds of the present invention include thyrotropin, polythyroid, KB-130015, and dronedarone.

Examples of suitable anabolic agents for use in combination with the compounds of the present invention include testosterone, TRH diethylstilbesterol, estrogens, β-agonists, theophylline, anabolic steroids, dehydroepiandrosterone, enkephalins, E-series prostagladins, retinoic acid and compounds as disclosed in U.S. Pat. No. 3,239,345,

e.g., Zeranol®; U.S. Patent No. 4,036,979, e.g., Sulbenox® or peptides as disclosed in U.S. Pat. No. 4,411,890.

The aforementioned patents and patent applications are incorporated herein by reference.

The above other therapeutic agents, when employed in combination with the compounds of the present invention, may be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

Where the compounds of the invention are utilized in combination with one or more other therapeutic agent(s), either concurrently or sequentially, the following combination ratios and dosage ranges are preferred:

When combined with a hypolypidemic agent, an antidepressant, a bone resorption inhibitor and/or an appetite suppressant, the compounds of formula I may be employed in a weight ratio to the additional agent within the range from about 500:1 to about 0.005:1, preferably from about 300:1 to about 0.01:1.

Where the antidiabetic agent is a biguanide, the compounds of formula I may be employed in a weight ratio to biguanide within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 2:1.

The compounds of formula I may be employed in a weight ratio to a glucosidase inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 50:1.

The compounds of formula I may be employed in a weight ratio to a sulfonylurea in the range from about 0.01:1 to about 100:1, preferably from about 0.2:1 to about 10:1.

The compounds of formula I may be employed in a weight ratio to a thiazolidinedione in an amount within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 5:1. The thiazolidinedione may be employed in amounts within the range from about 0.01 to about 2000 mg/day, which may optionally be administered in single or divided doses of one to four times per day. Further, where the sulfonylurea and thiazolidinedione are to be administered orally in an amount of less than about 150 mg, these additional agents may be incorporated into a combined single tablet with a therapeutically effective amount of the compounds of formula I.

Metformin, or salt thereof, may be employed with the compounds of formula I in amounts within the range from about 500 to about 2000 mg per day, which may be administered in single or divided doses one to four times daily.

The compounds of formula I may be employed in a weight ratio to a PPAR-alpha agonist, a PPAR-gamma agonist, a PPAR-alpha/gamma dual agonist, an SGLT2 inhibitor and/or an aP2 inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 5:1..

An MTP inhibitor may be administered orally with the compounds of formula I in an amount within the range of from about 0.01 mg/kg to about 100 mg/kg and preferably from about 0.1 mg/kg to about 75 mg/kg, one to four times daily. A preferred oral dosage form, such as tablets or capsules, may contain the MTP inhibitor in an amount of from about 1 to about 500 mg, preferably from about 2 to about 400 mg, and more preferably from about 5 to about 250 mg, administered on a regimen of one to four times daily. For parenteral administration, the MTP inhibitor may be employed in an amount within the range of from about 0.005 mg/kg to about 10 mg/kg and preferably from about 0.005 mg/kg to about 8 mg/kg, administered on a regimen of one to four times daily.

A HMG CoA reductase inhibitor may be administered orally with the compounds of formula I within the range of from about 1 to 2000 mg, and preferably from about 4 to about 200 mg. A preferred oral dosage form, such as tablets or capsules, will contain

the HMG CoA reductase inhibitor in an amount from about 0.1 to about 100 mg, preferably from about 5 to about 80 mg, and more preferably from about 10 to about 40 mg.

A squalene synthetase inhibitor may be administered with the compounds of formula I within the range of from about 10 mg to about 2000 mg and preferably from about 25 mg to about 200 mg. A preferred oral dosage form, such as tablets or capsules, will contain the squalene synthetase inhibitor in an amount of from about 10 to about 500 mg, preferably from about 25 to about 200 mg.

The compounds of formula I of the invention can be administered orally or parenterally, such as subcutaneously or intravenously, as well as by nasal application, rectally or sublingually to various mammalian species known to be subject to such maladies, e.g., humans, in an effective amount within the dosage range of abut 0.01 μg/kg to about 1000 μg/kg, preferably about 0.1 μg/kg to 100 μg/kg, more preferably about 0.2 μg/kg to about 50 μg/kg (or form about 0.5 to 2500 mg, preferably from about 1 to 2000 mg) in a regimen of single, two or four divided daily doses.

The compounds of the formula I can be administered for any of the uses described herein by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; bucally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally, including administration to the nasal membranes, such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents. The present compounds can, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release can be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. The present compounds can also be administered liposomally.

Examples of compositions for oral administration include suspensions which can contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which can contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The compounds of formula I can also be delivered through the oral cavity by sublingual and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Examples of compositions include those formulating the present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (avicel) or polyethylene glycols (PEG). Such formulations can also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g. Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Examples of compositions for nasal aerosol or inhalation administration include solutions in saline, which can contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Examples of compositions for parenteral administration include injectable solutions or suspensions which can contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid, or Cremaphor.

Examples of compositions for rectal administration include suppositories which can contain, for example, a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

Examples of compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

It will be understood that the specific dose level and frequency of dosage for any particular subject can be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition.

EXAMPLES

The following Examples represent preferred embodiments of the present invention. However, they should not be construed as limiting the invention in any way. The ^1H NMR spectra were consistent with the assigned structures. Mass spectra were recorded on a Perkin-Elmer, API 150Ex spectrometer, with turbo "ion spray" on negative ion mode (ES-1) or positive (ES+1), using a Zorbax SB-C8 column (LC-MS). Appropriate procedures for the preparation of methyl[3,5-chloro-4-(4-methoxy-3-isopropylphenoxy)] benzoate and methyl-N-[3,5-dichloro-4-(4-methoxy-3-isopropylphenoxy)benzoyl]glycine can be found in: "Novel Thyroid Receptor Ligands and Methods. Li, Y.-L.; Liu, Y.; Hedfors, A.; Malm, J.; Mellin, C.; Zhang, M. WO99/00353, PCT/EP98/04039" and "Novel diphenyl ether derivatives which are thyroid hormone beta-receptor ligands useful for treating metabolic disorders. Hangeland, J.; Zhang, M.; Caringal, Y.; Ryono, D.; Li,Y.-L.; Malm, J.; Liu, Y.; Garg, N.; Litten,C.; Garcia Collazo, A. M.; Koehler, K. WO00/039077, PCT/IB99/02084", respectively

Example 1: N-[3,5-Dichloro-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)benzoyl] glycine (E1)

(a) Nitric acid (2.84 mL, 65 %) was added to a stirred solution of methyl[3,5-dichloro-4- (3-isopropyl-4-methoxyphenoxy)] benzoate (2.84 g, 7.64 mmol) in benzene (200 mL). The resulting yellow reaction mixture was stirred at room temperature for three hours and then poured out in sodium hydrogencarbonate (saturated solution). The resulting organic and aqueous phases was separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases was dried over sodium sulfate and concentrated to give 2.40 g of a light yellow solid. The solid was solved in ethanol (150 mL, 95.5 %), sodium dithionite ($Na_2S_2O_4$, 85% purity, 7.12 g, 35.0 mmol) was added and the reaction mixture heated to reflux. After 16 hours, a second batch of sodium dithionite (3.00 g, 14.7 mmol) was added to the reaction mixture. After three hours, the reaction mixture was cooled down to room temperature, neutralized with sodium hydrogencarbonate (saturated solution) and concentrated. The residue was diluted with ethyl acetate (75 mL) and washed with water (50 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated to give a light yellow solid. The yellow solid was filtered through a short plug of silica, to give 2.2 g (75 %) of methyl[3,5-dichloro-4-(3-amino-5-isopropyl-4-methoxyphenoxy)] benzoate.

(b) A solution of sodium nitrite (0.30 g, 13 mmol) in water (5 mL) was added to a vigorously stirred mixture of methyl[3,5-dichloro-4-(3-amino-5-isopropyl-4-methoxy-phenoxy)] benzoate (1.1 g, 2.86 mmol), methanol (100 mL) and hydrochloric acid (75 mL, 37 %). The reaction mixture was stirred for one hour and then a solution of potassium iodide (1.43 g, 8.6 mmol) in water (5 mL) was added and the reaction mixture was stirred for 30 minutes. The temperature was kept at 0°C inside the flask during the whole course of reaction. After attaining room temperature the brownish reaction mixture was extracted with chloroform (3x 50 mL), the combined organic phases washed with sodium hydrogensulphate (saturated solution) followed by sodium thiosulphate (saturated solution). The organic phase was concentrated to give a dark red oily residue which was purified on column (silica gel, *n*-heptane/ethyl acetate 95:5), to

give 0.78 g (71 %) of methyl[3,5-dichloro-4-(3-iodo-5- isopropyl-4-methoxyphenoxy)] benzoate as a pale yellow mass.

(c) Methyl[3,5-dichloro-4-(3-iodo-5-isopropyl-4-methoxyphenoxy)] benzoate (0.500 mg, 1.01 mmol), tripotassium phosphate (1.07 g, 5.05 mmol), methyl boronic acid (0.303 mg, 5.05 mmol) and dioxane was mixed in a Schlenk tube under nitrogen gas. $PdCl_2$(dppf) was added to the tube under nitrogen gas and the reaction mixture was heated at 100°C for 16 hours. The reaction mixture was filtered through a short pad of silica and concentraded. The dark residue was purified on column (silica gel, *n*-heptane/ethyl acetate 95:5) to give a 85:15 mixture of methyl[3,5-dichloro-4-(3-isopropyl-4-methoxy-5-methylphenoxy)] benzoate and methyl[3,5-dichloro-4-(3-isopropyl-4-methoxyphenoxy)] benzoate. The mixture was obtained as a white solid mass (0.250 mg, 55 %) and was used without further purification in the next step.

(d) The mixture of methyl[3,5-dichloro-4-(3-isopropyl-4-methoxy-5-methylphenoxy)] benzoate and methyl[3,5-dichloro-4-(3-isopropyl-4-methoxyphenoxy)] benzoate above (250 mg) was solved in tetrahydrofuran (15 mL) and lithium hydroxide (1 N, 15 mL) was added. After 90 minutes stirring at room temperature, the reaction mixture was acidified with hydrochloride (1 N) and the aqueous and organic phase separated. The organic phase was dried over sodium sulfate and concentrated to give 0.250 g of a white solid mass, which was mixed with glycine methyl ester (164 mg, 1.30 mmol), 3-ethyl-1-[3-(dimethylamino)- propyl]carbodiimide hydrochloride (EDCI) (118 mg, 0.978 mmol) and N,N-dimethyl- formamide (20 mL). The reaction mixture was stirred for 10 minutes at room temperature, whereafter and 1-hydroxybenzotriazole hydrate (HOBt) (150 mg, 0.978 mmol) and triethyl- amine (0.272 mL, 1.96 mmol) was added. After 48 hours at room temperature, the reaction mixture was poured out in water (150 mL) and neutralized with hydrochloric acid (1 N). The aqueous phase was extracted with ethyl acetate (4x 100 mL), the collected organic phases dried over magnesium sulfate and concentrated. The residue was purified on column (silica gel, gradient elution: *n*-heptane/ethyl acetate from 7:3 to 5:5). This gave 165 mg (60 %) of

methyl-N-[3,5-dichloro-4-(5-isopropyl-4-methoxy-3-methylphenoxy)benzoyl]glycine as a white solid mass.

(e) Boron trifluoride dimethyl sulfide (1.48 mL, 13.7 mmol) was added at 4°C to a stirred solution of methyl-N-[3,5-dichloro-4-(5-isopropyl-4-methoxy-3-methylphenoxy)- benzoyl] glycine (155 mg, 0.352 mmol) and dichloromethane (15 mL). The reaction mixture was stirred at room temperature for 24 hours and then treated with ice-water (30 mL), extracted with ethyl acetate and concentrated. The residue was purified on column (MPLC, silica gel, chloroform/methanol/acetic acid, gradient elution from 1/0/0 to 95/5/0.5) to give 110 mg (76 %) of N-[3,5-dichloro-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)benzoyl] glycine. LC-MS (ES-1): m/z 410.

Example 2: N-[3,5-Dichloro-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E2)

(a) Borontribromide (1 N, in dichloromethane) was added to a solution of methyl-N-[3,5-dichloro-4-(4-methoxy-3-isopropylphenoxy)benzoyl]glycine (114 mg, 0.267 mmol) in dichloromethane (5 mL) at -78°C. The resulting brown reaction mixture was left at -25°C for 16 hours and at 4°C for two hours. A mixture of methanol (5 mL) and water (5 mL) was added at -70°C, the reaction mixture concentrated and diluted with ethyl acetate. The organic phase was washed with water, dried over sodium sulfate and concentrated. This gave 107 mg of methyl-N-[3,5-dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glycine as a beige solid mass.

(b) Bromine (33 µL) was added dropwise to a well stirred mixture of methyl-N-[3,5-dichloro-4-(4-hydroxy-3-isopropylphenoxy)benzoyl]glycine (240 mg, 0.582 mmol), acetic acid (4 mL), sodium acetate (88 mg, 0.64 mmol) and a few drops of water. The reaction mixture was stirred at room temperature for 16 hours, sodium thiosulfate (saturated) was added and the yellow mixture concentrated. The residue was diluted

with ethyl acetate and washed with water. The aqueous phase was extracted with dichloromethane, the combined organic phases washed with brine and dried over sodium sulfate. After concentration, 330 mg of a yellow sodid was obtained that was purified on column (silica gel, *n*-heptane/ethyl acetate, gradient elution from 100 % n-heptane to a mixture of 20 % n-heptane and 80 % ethyl acetate). This gave 200 mg (70 %) of methyl-N-[3,5-dichloro-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl]glycine as a white solid mass.

(c) Lithium hydroxide (1 N, 9 mL) was added at room temperature to a mixture of methyl-N-[3,5-dichloro-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl]glycine (150 mg, 0.305 mmol) and tetrahydrofuran (9 mL). After 16 hours, the reaction mixture was acidified with hydrochloric acid (1 N) and extracted with ethyl acetate. Filtration through a pad of silica gave N-[3,5-dichloro-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl]- glycine in quantitative yield as a light yellow solid. LC-MS (ES-1): m/z 476.

Example 3: N-[3,5-Dichloro-4-(2-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E3)

(a) Bromine (13 µL, 0.26 mmol) was added dropwise to a well stirred mixture of methyl-N-[3,5-dichloro-4-(4-methoxy-3-isopropylphenoxy)benzoyl]glycine (50 mg, 0.12 mmol), acetic acid (1.0 mL), sodium acetate (35 mg, 0.26 mmol) and a few drops of water. The reaction mixture was stirred at room temperature for three hours, heated at 40°C for 90 minutes and finally left at room temperature for 16 hours. Sodium acetate (17 mg) and bromine (6 µL) was added and the reaction mixture heated to 40°C for two hours. The reaction mixture was left at 4°C for three days. Sodium thiosulfate (saturated) was added and the yellow mixture concentrated. The residue was diluted with ethyl acetate and washed with water. The aqueous phase was extracted with dichloromethane, the combined organic phases washed with brine and dried over sodium sulfate. After concentration, the residue was purified on column (hplc, C_8, acetonitrile/water/formic acid, gradient elution from 20/80/0.5 to 100/0/0) to give 1.0 mg (2 %) of methyl-N-[3,5-dichloro-4-(2-bromo-4-methoxy-5-isopropylphenoxy)benzoyl]glycine.

(b) Boron trifluoride dimethyl sulfide (10 µL, 80 µmol) was added at room temperature to a stirred solution of methyl-N-[3,5-dichloro-4-(2-bromo-4-methoxy-5-isopropylphenoxy)- benzoyl] glycine (1.0 mg, 2.0 µmol) and dichloromethane (0.50 mL). The reaction mixture was stirred at room temperature for 8 hours and then treated with ice-water, extracted with ethyl acetate and washed with water. The organic phase was dried over sodium sulphate and concentrated to give a light yellow solid. The solid was purified on column (MPLC, silica gel, chloroform/methanol/acetic acid, gradient elution from 1/0/0 to 95/5/0.5) to give 0.90 mg (94 %) of N-[3,5-dichloro-4-(2-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine. LC-MS (ES-1): m/z 476.

Example 4: N-[3,5-Dichloro-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E4)

(a) Methyl[3,5-dichloro-4-(3-isopropyl-4-methoxyphenoxy)] benzoate (664 mg, 1.8 mmol) dissolved in acetone (40 mL), was added during 5 minutes at 0°C to a stirred mixture of calcium hypochlorite (515 mg, 3.6 mmol), water (10 mL) and acetic acid (4 mL). The reaction mixture was stirred at 0°C for 30 minutes and then 30 minutes at room temperature. The reaction mixture was poured out in water, extracted with ethyl acetate (3x 50 mL), the combined organic phases washed with water (4x 30 mL) and concentrated. The residue was purified on column (silica gel, n-heptane/ethyl acetate, gradient elution from 98:2 to 90:10) to give 240 mg (60 %) of methyl[3,5-dichloro-4-(3-chloro-5-isopropyl-4-methoxyphenoxy)] benzoate. The calcium hypochlorite used in this step could be exchanged to t-butyl hypochlorite.

(b) Methyl[3,5-dichloro-4-(3-chloro-5-isopropyl-4-methoxyphenoxy)] benzoate, methanol (25 mL) and sodium hydroxide (6 N, 4 mL) was stirred at room temperature for 8 hours. The reaction mixture was neutralized with aqueous hydrochloric acid and extracted with ethyl acetate (3x 30 mL). The combined organic phases were washed with water, concentrated and the residue titurated with *n*-heptane. This gave 133 mg (58

%) of 3,5- dichloro-4-(3-chloro-5- isopropyl-4-methoxyphenoxy)benzoic acid obtained as a white solid.

(c) Glycine methyl ester hydrochloride (83 mg, 0.66 mmol) and triethylamine (100 mg, 0.99 mmol) was added to a stirred mixture of 3,5-dichloro-4-(3-chloro-5-isopropyl-4-methoxyphenoxy)benzoic acid (130 mg, 0.33 mmol), EDCI (88 mg, 0.46 mmol), HOBt (86 mg, 0.56 mmol) and *N,N*-dimethylformamide (15 mL). The reaction mixture was stirred for 48 hours at room temperature, poured out in a mixture of hydrochloric acid (1 N, 5.0 mL) and water (50 mL), and extracted with ethyl acetate (4x 20 mL). The collected organic phases dried was washed with water (4x 15 mL), the organic phase concentrated and the residue purified on column (silica gel, *n*-heptane/ethyl acetate, gradient elution from 90:10 to 75:25). This gave 90 mg (59 %) of methyl-N-[3,5-dichloro-4-(3-chloro-5-isopropyl-4-methoxy- phenoxy)benzoyl] glycine.

(d) Boron trifluoride dimethyl sulfide (1.0 mL) was added at room temperature to a stirred solution of methyl-N-[3,5-dichloro-4-(3-chloro-5-isopropyl-4-methoxyphenoxy)benzoyl] glycine (90 mg) and dichloromethane (10 mL). The reaction mixture was stirred at room temperature for 24 hours, poured out in water and extracted with ethyl acetate (3x 30 mL). The combined organic phases were washed with water (4x 20 mL), concentrated and the resulting residue purified on column (silica gel, chloroform/methanol/acetic acid 94:6:0.65). This gave 53 mg (63 %) of N-[3,5-dichloro-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine. LC-MS (ES+1): m/z 434.

Example 5: N-[3,5-Dichloro-4-(3-cyano-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E5)

(a) Methyl [3,5-dichloro-4-(3-iodo-5-isopropyl-4-methoxyphenoxy)] benzoate (for preparation see ex.1 a-b) (200 mg, 0.40 mmol), copper cyanide (50 mg, 0.56 mmol) and DMF (4ml) was heated to 120°C for 16h. After attaining room temperature, the dark reaction mixture was quenched by saturated sodium hydrogencarbonate solution and

extracted with ethyl acetate. The organic phase was dried over sodium sulfate and concentrated. The residue was purified on column (MPLC, silica gel, gradient elution: *n*-heptane/ethyl acetate from 1:0 to 9:1) to give 65 mg (41 %) of methyl [3,5-dichloro-4-(3-cyano-5-isopropyl-4-methoxyphenoxy)] benzoate.

(b) Borontribromide (1 N in dichloromethane, 0.93mL) was added to a solution of methyl [3,5-dichloro-4-(3-cyano-5-isopropyl-4-methoxyphenoxy)] benzoate (32 mg, 81µmol) in dichloromethane (0.75mL) at -78°C. After 20h at -25°C and 16h at room temperature, the reaction mixture was quenched by ice water at 0°C and the organic solvent was removed by evaporation. The residue was acidified by hydrochloric acid (1 N) and extracted by ethyl acetate. The organic phase was dried over sodium sulfate and filtrated through a pad of silica. The resulting yellow solid was mixed with glycine methyl ester (23 mg, 0.18 mmol), EDCI (35 mg, 0.18 mmol) and N,N-dimethylformamide (1 mL). The reaction mixture was stirred for 10 minutes at room temperature, whereafter HOBt (28 mg, 0.18 mmol) and triethylamine (38µL, 0.27 mmol) was added. After 16 hours at room temperature, the reaction mixture was poured out in water (5 mL) and neutralized with hydrochloric acid (1 N). The aqueous phase was extracted with ethyl acetate (2x 10 mL) and the collected organic phases was dried over sodium sulfate and concentrated. The residue was purified on column (MPLC, silica gel, gradient elution: *n*-heptane/ethyl acetate from 9:1 to 7:3). This gave 15 mg (42 %) of methyl-N-[3,5-dichloro-4-(3-cyano-4-hydroxy-5-isopropylphenoxy)benzoyl]glycine as a white solid mass.

(c) Borontribromide (1 N in dichloromethane, 0.11mL) was added to a solution of methyl-N-[3,5-dichloro-4-(3-cyano-4-hydroxy-5-isopropylphenoxy)benzoyl]glycine (7 mg, 16µmol) in dichloromethane (0.5mL) at -78°C. The resulting reaction mixture was stirred at room temperature for 16h and thereafter quenched by ice water. The organic solvent was removed with evaporation and the remaining residue was acidified by hydrochloric acid (1 N) and extracted by ethyl acetate. Drying over sodium sulfate, concentration and purification on a silica SPE column (0.5g, 3mL, gradient elution: chloroform/methanol/acetic acid from 1:0:0 to 98:2:0.5) gave 3 mg (44%) of

N-[3,5-dichloro-4-(3-cyano-4-hydroxy-5-isopropyl-phenoxy)benzoyl]glycine. LC-MS (ES-1): m/z 421.

Example 6: N-[3,5-Dichloro-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine (E6)

(a) To a solution of methyl [3,5-dichloro-4-(3-isopropyl-4-methoxyphenoxy)] benzoate (2.0 g, 5.4 mmol) in benzene (200 ml), nitric acid (2.07 ml, 65%) was added drop wise. The mixture was further stirred for 1h at room temperature. The reaction was monitored by TLC (65:35 *n*-heptane/ethyl acetate) and the mixture was quenched with saturated aqueous solution of sodium hydrogencarbonate. The resulting organic and aqueous phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with water, brine, and the organic phase was dried over magnesium sulfate, and concentrated. The crude product was crystallize from methanol to give 1.8g, (80%) of methyl[3,5-dichloro-4-(5-isopropyl-4-methoxy-3-nitrophenoxy)] benzoate.

(b) To the solution of methyl[3,5-dichloro-4-(5-isopropyl-4-methoxy-3-nitrophenoxy)] benzoate (500mg, 1.21mmol) in tetra hydrofuran (10mL), lithium hydroxide (5mL, 1M) was added. The mixture was stirred over night at room temperature. The reaction mixture was acidified with hydrochloric acid (1 N) and the aqueous and organic phase separated. The aqueous phase extracted with ethyl acetate. The combined organic phase was washed with water and dried over magnesium sulfate and concentrated. The crude product was purified on column (silica gel, chloroform/methanol/acetic acid 98: 2: 0.3) to give 418mg (86%) of 3,5-dichloro-4-(5-isopropyl-4-methoxy-3-nitrophenoxy) benzoic acid.

(c) Glycine methyl ester hydrochloride (262mg, 2.08 mmol) and triethylamine (317 mg, 3.13 mmol) was added to a stirred mixture of 3,5-dichloro-4-(5-isopropyl-4-methoxy-3-nitrophenoxy)] benzoic acid (418mg, 1.04mmol)), EDCI (401mg, 2.08mmol), HOBt (320mg, 2.08 mmol) in *N,N*-dimethylformamide (50 mL). The reaction mixture was stirred for 24 hours at room temperature, poured out in a mixture of hydrochloric acid (1 N, 10 mL) and water

(50 mL), and extracted with ethyl acetate. The collected organic phases dried was washed with water, the organic phase concentrated and the residue was purified on column (silica gel, *n*-heptane/ethyl acetate, gradient elution from 98:2 to 60:40) to give 380 mg (78 %) of methyl-N-[3,5-dichloro-4-(5-isopropyl-4-methoxy-3-nitro-phenoxy)benzoyl] glycine.

(d) A mixture of methyl-N-[3,5-dichloro-4-(5-isopropyl-4-methoxy-3-nitro-phenoxy)benzoyl] glycine (380 mg, 0.81 mmol) and PtO_2 (40 mg) in ethyl acetate (10 mL) was stirred at room temperature under hydrogen (atmospheric pressure) for 24h. Pt catalyst was removed by filtration through celite and the filtrate was concentrated, which was purified on column (silica gel, *n*-heptane/ethyl acetate, gradient elution from 98:2 to 60:40) to give 320mg (89%) of methyl-N-[3,5-dichloro-4-(3-amino-5-isopropyl-4-methoxyphenoxy)benzoyl] glycine.

(e) A solution of nitrosonium tetrafluoroborate (55mg, 0.47mmol) in dichloromethane (5mL) was cooled to 0 °C and methyl-N-[3,5-dichloro-4-(3-amino-5-isopropyl-4-methoxyphenoxy) benzoyl] glycine (189mg, 0.43mmol) was added. The reaction mixture was further stirred at 0 °C for 1h. Dichloromethane was removed from nitrogen and o-xylene (10mL) was added to the reaction mixture. The reaction mixture was refluxed for 1h and the solvent was removed. The crude reaction mixture was purified on column (silica gel, *n*-heptane/ethyl acetate, gradient elution from 98:2 to 60:40) to give 50mg (26%) of methyl-N-[3,5-dichloro-4-(3-fluro-5-isopropyl-4-methoxyphenoxy)benzoyl] glycine.

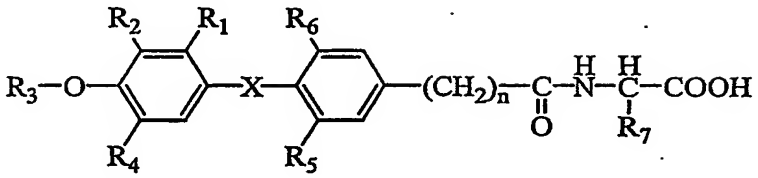
(f) Boron trifluoride dimethyl sulfide (2.0 mL) was added at room temperature to a stirred solution of methyl-N-[3,5-dichloro-4-(3-fluro-5-isopropyl-4-methoxyphenoxy)benzoyl] glycine (50 mg, 0.11mmol) and dichloromethane (8 mL). The reaction mixture was stirred at room temperature for 24 hours, poured out in water and extracted with ethyl acetate. The combined organic phases were washed with water, concentrated and the resulting residue purified on column (HPLC, ACE-C_8, acetonitrile/0.05%formic acid in water,

gradient elution from 5/95 to 60/40) to give 5 mg (20 %) of N-[3,5-dichloro-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine. LC-MS (ES-1): m/z 414.

The compounds of Examples 1-6 exhibit binding affinities to the thyroid receptor beta in the range of IC_{50} of 1.0 to 100 nM.

CLAIMS

1. A compound of the general formula:



I

or a pharmaceutically acceptable salt thereof, wherein:

R_1 and R_2 are independently selected from: hydrogen, fluorine, chlorine, bromine, nitrile (-CN), C_{1-2} alkyl, said alkyl substituted with 0, 1, 2 or 3 R^a groups which may be the same or different, and with the proviso that R_1 and R_2 are not both hydrogen.

R_3 is selected from: hydrogen, C_{1-6} alkyl or benzyl, said alkyl or benzyl being substituted with 0, 1, 2 or 3 R^a groups which may be the same or different;

R_4 is selected from: halogen; C_{1-4} alkyl, C_{3-4} cycloalkyl, C_{2-4} alkenyl and C_{2-4} alkynyl, said alkyl, cycloalkyl, alkenyl and alkynyl being substituted with 0, 1, 2 or 3 R^a groups which may be the same or different;

R_5 and R_6 are the same or different and are independently selected from: chlorine, bromine, and C_{1-4} alkyl;

R_7 is selected from: hydrogen; C_{1-4} alkyl, C_{3-4} cycloalkyl, C_{2-4} alkenyl and C_{2-4} alkynyl, said alkyl, cycloalkyl, alkenyl and alkynyl being substituted with 0, 1, 2 or 3 R^a groups which may be the same or different;

R^a is fluorine, chlorine or bromine;

n is 0, 1 or 2;

X is selected from: -O-, -S-, -SO-, $-SO_2-$, $-SO_2NH-$ and $-SO_2O-$;

and pharmaceutically acceptable salts, prodrug ester forms and stereoisomers thereof.

2. A compound according to claim 1, which has one or more assymetric centers.

3. A compound according to claim 1 or 2 said compound being:
N-[3,5-Dichloro-4-(4-hydroxy-3-isopropyl-5-methylphenoxy)benzoyl] glycine **(E1)**;
N-[3,5-Dichloro-4-(3-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine **(E2)**;
N-[3,5-Dichloro-4-(2-bromo-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine **(E3)**;
N-[3,5-Dichloro-4-(3-chloro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine **(E4)**;
N-[3,5-Dichloro-4-(3-cyano-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine **(E5)**;
N-[3,5-Dichloro-4-(3-fluoro-4-hydroxy-5-isopropylphenoxy)benzoyl] glycine **(E6)**.

4. A compound according to any of claims 1 to 3 for use in medical therapy.

5. A pharmaceutical composition comprising an effective amount of a compound according to any of claims 1 to 3 or a pharmaceutically effective salt thereof, together with a pharmaceutically acceptable carrier.

6. A process for making a pharmaceutical composition comprising combining a compound according to any of claims 1 to 3 and a pharmaceutically acceptable carrier.

7. A pharmaceutical composition comprising at least one compound according to any of claims 1 to 3 and at least one additional therapeutic agent selected from anti-diabetic agents, anti-osteoporosis agents, anti-obesity agents, growth promoting agents, anti-inflammatory agents, anti-anxiety agents, anti-depressants, anti-hypertensive agents, cardiac glycosides, cholesterol/lipid lowering agents, appetite supressants, bone resorption inhibitors, thyroid mimetics, anabolic agents, anti-tumor agents and retinoids.

8. The pharmaceutical composition of claim 7 wherein said additional therapeutic agent is an antidiabetic agent selected from biguanides, glucosidase inhibitors, meglitinides, sulfonylureas, thiazolidinediones, PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, SGLT2 inhibitors, glycogen phosphorylase inhibitors, aP2 inhibitors, glucagon-like peptide-1 (GLP-1)s, and dipeptidyl peptidase IV inhibitors.

9. The pharmaceutical composition of claim 7 wherein said additional therapeutic agent is an antidiabetic agent selected from metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, troglitazone, pioglitazone, englitazone, darglitazone, rosiglitazone and insulin.

10. The pharmaceutical composition of claim 7 wherein said additional therapeutic agent is an anti-obesity agent selected from aP2 inhibitors, PPAR gamma antagonists, PPAR delta agonists, beta 3 adrenergic agonists, lipase inhibitors, serotonin reuptake inhibitors and anorectic agents.

11. The pharmaceutical composition of claim 7 wherein said additional therapeutic agent is a hypolipidemic agent selected from thiazolidinediones, MTP inhibitors, squalene synthetase inhibitors, HMG CoA reductase inhibitors, fibric acid derivatives, ACAT inhibitors, cholesterol absorption inhibitors, ileal Na^+/bile cotransporter inhibitors, bile acid sequestrants and a nicotinic acid or a derivative thereof.

12. A method for preventing, inhibiting or treating a disease which is dependent on the expression of a T_3 regulated gene or associated with metabolic dysfunction, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in claims 1 to 3.

13. The method as defined in claim 12, wherein the said disease is obesity, hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer, glaucoma, cardiac arrhythmia, congestive heart failure, or skin disorders.

14. The method according to claim 13, wherein the skin disorder or disease is dermal atrophy, post surgical bruising caused by laser resurfacing, keloids, stria, cellulite, roughened skin, actinic skin damage, lichen planus, ichtyosis, acne, psoriasis, Dernier's disease, eczema, atopic dermatitis, chloracne, pityriasis and skin scarring.

15. The use of a compound according to claims 1 to 3 in the preparation of a medicament for the treatment of a disease or disorder which is dependent on the expression of a T_3 regulated gene.

16. The use according to claim 15 wherein said disease or disorder is obesity, hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism, goiter, thyroid cancer, and other endocrine disorders related to thyroid hormone.

17. The use according to claim 15 wherein said disease or disorder is a skin disorder, glaucoma, cardiovascular disease, or congestive heart failure.

18. The use according to claim 17, wherein the skin disorder is dermal atrophy, post surgical bruising caused by laser resurfacing, keloids, stria, cellulite, roughened

skin, actinic skin damage, lichen planus, ichtyosis, acne, psoriasis, Dernier's disease, eczema, atopic dermatitis, chloracne, pityriasis and skin scarring.

19. A method to treat certain skin disorders or diseases by the use of a compound of claims 1 to 3 in a combination with a retinoid or a Vitamin D analog.

ABSTRACT OF DISCLOSURE

This invention relates to novel compounds, which are thyroid receptor ligands, and are preferably selective for the thyroid hormone receptor β and to methods of preparing such compounds. In addition, a method is provided for preventing, inhibiting or treating diseases or disorders associated with metabolism dysfunction or which are dependent upon the expression of a T_3 regulated gene, wherein a compound as described herein is administered in a therapeutically effective amount.

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